23653

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU2005/000002	25.01.2005	27.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D233/60, A61K31/4174, A61P31/10

Applicant
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1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-10
	No:	Claims	1, 2, 11
Inventive step (IS)	Yes:	Claims	3-10
	No:	Claims	1, 2, 11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: WALKER K A M ET AL: "1-[4-(4-Chlorophenyl)-2-(2,6-dichloro phenylthio)-n-butyl]-1H-imidazole nitrate, a new potent antifungal agent" JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 8, August 1978 (1978-08), pages 840-843, XP002325101

Novelty (Article 33(2) PCT)

D1 discloses butoconazole nitrate having a melting point of 162-163°C. It is considered that the disclosure of the low-molecular weight butoconazole nitrate effectively discloses this compound in any degree of purity, because the skilled reader would dispose of a plurality of standard methods to achieve any desired purity.

Similarly, numerous methods are known to prepare a solid compound in any desired particle size.

The subject-matter of claims 1, 2 and 11 lacks therefore novelty.

The processes of claims 3-10 are not disclosed in the available prior art.

Inventive step (Article 33(3) PCT)

The subject-matter of claims 1, 2 and 11 lacks novelty and does therefore not offer a basis for acknowledging an inventive step.

For the subject-matter of claims 3-10 an inventive step can be acknowledged:

D1, which is considered to represent the closest prior art, describes a process for preparing butoconazole nitrate by condensation of 1-chloro-4-(4-chlorophenyl)-2-butanol

with imidazole in the presence of NaH in DMF (first step), conversion of the obtained alcohol to the chloride using neat thionyl chloride (second step), reaction of the obtained chloride with dichlorothiophenol and conversion to the nitrate salt.

In the light of the teachings of D1, the problems underlying and solved by the present application can be seen in an improved process for preparing butoconazole nitrate, and in a process for preparing this compound as small particles.

The use of a transfer catalyst in the first step and of 1,2-dichloroethane in the second step are not suggested in the available prior art, and are not obvious measures to solve the given problem.

The precipitation of butoclonazole nitrate from its solution in MeOH/methyl isobutyl ketone is not suggested in the available prior art to obtain small particles of said compound.

Industrial applicability (Article 33(4) PCT)

The compounds, composition and processes of claims 1-11 can be used in the pharmaceutical industry.